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The heterogeneity hidden in allergic rhinitis and its impact on coexisting asthma in adults: a population-based survey

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10 **adults: a population-based survey.**

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15 **TITLE**

16 **The heterogeneity hidden in allergic rhinitis and its impact on coexisting asthma in**
17 **adults: a population-based survey**

18

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41 **RUNNING TITLE: The heterogeneity of allergic rhinitis**

42

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52

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62

63 **Abstract:**

64 **Background:** It has been suggested that there is some overlap between allergic rhinitis
65 (AR), sinusitis and polyposis but it has not been fully documented.

66 This study aimed to evaluate the prevalence of these coexisting diseases and their impact
67 on bronchial asthma in the general population in Italy.

68 **Methods:** In the frame of the multicentre Gene Environment Interactions in Respiratory
69 Diseases (GEIRD) study, a postal screening questionnaire including questions about self
70 reported symptoms of asthma, AR, AR with Sinusitis without Nasal Polyps (AR+SsNP)
71 and ARwith Sinusitis with Nasal Polyps (AR+SwNP) was administered. Random samples
72 of subjects aged 20-44 years (n=5162) answered the postal questionnaire in 4 Italian
73 centres (Pavia, Sassari, Torino, Verona). In allergic rhinitis subjects, the association
74 among AR only, AR+SsNP, AR+SwNP, and bronchial asthma was estimated by the
75 Relative Risk Ratio (RRR) using multinomial regression models.

76 **Results:** The prevalence of AR in the sample was 25.4% (95%CI:24.2-26.6). The self-
77 reported diagnosis of AR+SsNP and AR+SwNPwas reported by 5.7% (95%CI:5.0-6.3) and
78 by 1.2% (95%CI:0.9-1.5) of the subjects respectively. Current asthma was reported by
79 17.5% of the AR subjects. In the adjusted multivariate analysis, the risk of having current
80 asthma (RRR=2.31; 95%CI:1.29-4.15), of having at least 1 asthma attack/year
81 (RRR=2.30; 95%CI:1.19-4.46) and of having an emergency department admission for
82 respiratory diseases (RRR=5.61; 95%CI:1.81-23.92) was higher for subjects with
83 AR+SwNP , than subjects with AR only.

84 **Conclusions:** The diagnosis of allergic rhinitis in the epidemiological setting includes
85 heterogeneous upper airway diseases that affect the clinical features of AR and its
86 interactions with asthma.

87

88

89 **Introduction**

90 Allergic rhinitis (AR) is the most common immunologic disease and its prevalence is
91 continuously on the increase, in particular in Western countries [1-3]. This not only affects
92 the burden of the disease on patients [1-4], but it also has an impact on bronchial asthma
93 and subsequently leads to an increased cost in health care use [1,6].

94 In epidemiology, validated questionnaires are used for the diagnosis of allergic rhinitis. An
95 Italian study showed that the reliability of the question on allergic rhinitis seems adequate
96 for epidemiological purposes and about 20% of the subjects who answered positively to
97 the question on allergic rhinitis had had a negative skin prick test or specific IgE levels [7].

98 Studies focusing on the non-allergic upper airway diseases (such as chronic rhinitis and
99 rhinosinusitis, with and without nasal polyps) showed the importance of the association
100 between these diseases and severe/not controlled asthma suggesting that these upper
101 airway diseases have a greater impact on asthma compared to allergy [8-12].

102 The overlap between allergic and non allergic upper airways diseases has been discussed
103 in clinical studies, but its epidemiological results remain controversial and poorly defined
104 [13-15].

105 This study aimed to evaluate the prevalence of AR, AR with Sinusitis without Nasal Polyps
106 (AR+SsNP), AR with Sinusitis and with Nasal Polyps (AR+SwNP) and if the interaction
107 between AR and bronchial asthma has been affected by concomitant upper airway
108 diseases.

109

110 **Materials and Methods**

111 The study Gene Environment Interactions in Respiratory Diseases (GEIRD), is a
112 multicentre survey on respiratory health in the general adult population, carried out
113 between 2007 and 2010. In the frame of this study, random samples of about 3000
114 subjects from the general population aged 20 to 44 years old (male/female ratio=1) were
115 selected from the registry of the local health authority in each of the four Italian centres:
116 Pavia, Sassari, Torino, Verona [16].

117 A screening questionnaire on respiratory symptoms was administered to eligible subjects
118 by mail up to three times in case of non response and once by phone for subjects who had
119 not responded by mail.

120 The GEIRD screening questionnaire (available in www.geird.org), a modified version of
121 questionnaires used in previous studies [17] included self reported information about
122 respiratory symptoms (asthma, rhinitis and chronic bronchitis, cough and phlegm),
123 environmental exposures (smoking habits) and education level as a proxy of socio-
124 economic status.

125

126 *Definitions and conditions*

127 The presence of AR was based on the answer to the questionnaire: “Do you have any
128 nasal allergies including hay fever?”. Subjects who answered “yes” were classified as
129 subjects with AR. If a subject answered “no” to the question he/she was classified as a
130 subject without allergic rhinitis.

131 Subjects with allergic rhinitis subjects were further classified as follows:

- 132 • AR only: subjects with AR but without sinusitis (S) or Nasal Polyps (NP);
- 133 • AR+SsNP: subjects with AR and who also answered “yes” to the question: “Do
134 you suffer from sinusitis?”;

- AR+SwNP: subjects with AR and Sinusitis and who also answered “yes” to the question: “Do you suffer from nasal polyps?”.

The presence of asthma was defined as :

- physician-diagnosed asthma if he/she answered “yes” to both of the following questions: “Have you ever had asthma?” and “Was this confirmed by a doctor?”;
- current asthma if he/she had physician-diagnosed asthma and took any medicines for asthma and had had an attack of asthma or at least one among the following asthma-like symptoms: wheezing, chest tightness, shortness of breath, in the last 12 months.

As indicators of asthma severity/control we used:

- the number of asthma attacks reported by the subject in the last 12 months classified as: “at least 1 asthma attack” and “>3 asthma attacks” ;
- the presence of the asthma-*chronic obstructive pulmonary disease (COPD)* overlap syndrome, when a subject with current asthma answered “yes” to the following question: “Have you ever been told by a doctor that you have or had chronic bronchitis, COPD or emphysema?”
- the intake of drugs for rhinitis and asthma based on the answers to the following questions: “Have you used any medicines for asthma in the last 12 months (including inhalers, aerosols or tablets)?” and “Have you used any medicines for rhinitis in the last 12 months (including inhalers, aerosols or tablets)?”.

A four level variable was computed to evaluate which type of drugs a subjects used:

“no medicines” if a subject answered “no” to both questions; “only asthma medicines” if a subjects took medicines for asthma and had not taken medicine for rhinitis in the last 12 months; “only rhinitis medicines” if a subjects took medicines for rhinitis and had not taken medicine for asthma in the last 12 months;

“both” if a subject had taken medicines for both rhinitis and for asthma in the last 12 months.

The presence of chronic cough and phlegm assessed by a positive answer to the question “Have you had coughing and phlegm on most days for a minimum of 3 months a year and for at least 2 successive years?”

Also, a subject has been to Emergency Department (ED) for respiratory diseases if he/she answered “yes” to both of the following questions: “In the past 3 months have you been to Emergency Department for any reason, excluding accidents and injuries?” and “Was it due to respiratory problems?”.

Confounders

The potential confounders considered in the analysis were: gender, age (<30,30-39,≥40 years), smoking habits (never smoker, ex smoker, current smoker), level of education (primary and lower secondary school, upper secondary school, degree), season of response (spring, summer, autumn, winter). In addition, type of contact (mail, phone), percentile rank of cumulative response centre-specific and centre were included as design confounders in the analysis.

Statistical analysis

Categorical variables were summarized with percentages, and were compared across strata by the Pearson’s Chi-squared test.

The associations among different allergic rhinitis overlapping diseases (AR only, AR+SnNP, AR+SwNP), and other outcomes (diagnosed and current asthma, number of asthma attacks, asthma-COPD overlap syndrome, cough and phlegm and ED visits for respiratory diseases), were assessed by using multinomial regression models adjusted for potential confounders (gender, age, smoking habits, level of education, season of

186 response, type of contact, percentile rank of cumulative response and centre). The
187 Relative Risk Ratio (RRR) was estimated by choosing the group with AR only as the
188 reference category. A p-value <0.05 was considered statistically significant. Statistical
189 analyses were performed with STATA 12.1 (Stata Corp LP, College Station, TX, USA).
190

191 **Results**

192 *Prevalence of allergic rhinitis and demographic data*

193 Overall 5162 subjects filled in the questionnaire in the 4 centres. The response rate was
194 53%, ranging from 37.1% (Pavia) to 67.7% (Verona). The overall prevalence of allergic
195 rhinitis in the study was 25.4% (95%CI 24.2-26.6). The subjects who self-reported
196 diagnosis of AR+SsNP and AR+SwNP were 5.7% and 1.2% respectively.

197 The subjects with AR were younger (table 2), fewer current smokers and they had a higher
198 level of education than those without AR. The distribution of sex and education level
199 among the three different groups of upper airway diseases (AR only, AR+SsNP and
200 AR+SwNP) was statistically significant. The percentage of females was lower in subjects
201 with AR+SwNP (36.1%) compared to the other two groups (51.8% and 63.5% for AR and
202 AR+SsNP respectively). The level of education was significantly lower for subjects with
203 AR+SwNP than for those of the other two groups ($p=0.019$).

204

205 *Overlapping upper airway diseases and asthma*

206 Overall, 23.8% of the subjects with AR had a physician diagnosed asthma and 17.5% of
207 the subjects reported current asthma at the time of the survey (table 3). The prevalence of
208 current asthma and the distribution of the control/severity markers of coexisting asthma
209 varied significantly across the three different groups of AR subjects. In particular, the
210 prevalence of current asthma increased from 15.8% in the group of AR only to 31.2% in
211 the group AR+SwNP ($p<0.001$). The same statistically significant trend was found when
212 considering the proportion of subjects who had at least one asthma attack in the last 12
213 months ($p=0.01$), of subjects with the asthma-COPD overlap syndrome ($p=0.03$), of
214 subjects with chronic cough and phlegm ($p<0.001$) and of those who had been
215 hospitalized for respiratory diseases ($p<0.01$).

216 The only exception to this general trend was the prevalence for subjects who had had
217 more than three asthma attacks/year which, was similar in the three groups of upper
218 airway diseases ($p=0.76$).

219 In the multivariate analysis (table 4), after adjusting for potential confounders, the subjects
220 with AR+SwNP, had a statistically significant increased risk of having current asthma
221 ($RRR=2.31$; $95\%CI:1.29-4.15$), of having at least one asthma attacks in the last year
222 ($RRR=2.30$; $95\%CI: 1.19-4.46$) and of having an ED admission for respiratory disease in
223 the last 3 months ($RRR= 5.61$; $95\%CI: 1.81-23.92$) than subjects with AR only.

224 Finally, the subjects with AR+SsNP and AR+SwNP had a statistically significant increased
225 risk of having cough and phlegm ($RRR=2.59$; $95\%CI: 1.89-3.54$ and $RRR=2.91$; $95\%CI:$
226 $1.63-5.21$ respectively) than subjects with AR only, while the asthma-chronic bronchitis
227 overlap syndrome did not show statistically significant variations among the AR groups.

228

229 *Overlapping upper airway diseases and drug intake for rhinitis and asthma.*

230 Overall, 54% and 17.5% of subjects with AR had used medication for rhinitis and asthma
231 respectively in the last year. After adjusting for potential confounders, in the multivariate
232 analysis we found an increased risk that the subjects with AR+SsNP and AR+SwNP took
233 medications both for rhinitis ($RRR=1.91$; $95\%CI: 1.43-2.54$ and $RRR=2.46$; $95\%CI: 1.38-$
234 4.40 respectively) and for asthma ($RRR=1.52$; $95\%CI: 1.08-2.15$ and $RRR=2.27$; $95\%CI:$
235 $1.23-4.19$ respectively) than subjects with AR only.

236 The overall distribution of the drugs intake for rhinitis and/or asthma across the three
237 different groups of AR subjects is shown in the figure 1. The proportion of subjects who
238 had not used medication in the last 12 months decreased from 46% in subjects with AR
239 only to 28% in those with AR+S+P, whereas the use of medication for both rhinitis and
240 asthma increased from 11% in the subjects with AR only to 28% in the subjects with
241 AR+SwNP ($p<0.001$).

242 When we considered the distribution of the drugs used only by the subjects with current
243 asthma, stratified by no asthma attacks and at least one asthma attack, we found that the
244 proportion who used drugs for asthma or for rhinitis was almost 65% in those who had not
245 had an asthma attack and almost 95% in those who had had at least one asthma attack.
246 The distribution of drugs used among the three groups of upper airway diseases was
247 similar both for subjects with no asthma attack and at least one asthma attack (figure 2).

248

249

250

251 **Discussion**

252 The most important finding of the study was that AR coexisted with sinusitis, with and
253 without nasal polyps, in 6.9% of the general population. In addition, subjects with
254 AR+SwNP had a higher likelihood of having more severe asthma than those with AR only.
255 We also discuss the reliability of a self-reported diagnosis of sinusitis and the identification
256 of subjects with nasal polyps as a subgroup of those with AR.

257

258 *Prevalence of the upper airway diseases.*

259 Overall, about 25% of the subjects reported AR, about 6% reported AR plus sinusitis with
260 and without nasal polyps and these prevalence were similar across the centres.

261 Concerns about the self-reported diagnosis of chronic rhinosinusitis [18,19] have led to the
262 development of a specific questionnaire, to diagnose chronic rhinosinusitis in the
263 epidemiological setting [20].

264 A recent postal survey performed in Europe, using the EP3OS criteria questionnaire, found
265 that the prevalence of chronic rhinosinusitis in the general population was 10.9%, with
266 relevant variations of prevalence in the different geographical areas. In the only Italian
267 center participating in this survey (Palermo) the prevalence was 10.8% (6,9% self-reported
268 doctor-diagnosis) [21].

269 In the EP3OS study, the diagnosis of chronic rhinosinusitis includes patients with and
270 without nasal polyps, while the diagnosis of chronic rhino-sinusitis is limited only to the
271 young adult subjects with AR in our survey. Although the diagnosis of sinusitis was only
272 assessed in subjects with AR and consisted of a single question in the questionnaire, we
273 might suppose that the prevalence of AR+SsNP found in our survey is coherent with that
274 found in Italy.

275 The prevalence of AR+SwNP found in our survey is in line with the estimated prevalence
276 found both in Europe, which ranged from 2 to 4% of the general populations [22] and

277 found in a specific survey in France (2.1%) [23]. However other studies [24] found a higher
278 prevalence of polyposis than our survey but this could be due to the fact that the it was not
279 in a population-based study.

280 Overall, the reliability of the self-reported diagnosis of chronic rhinosinusitis and of
281 AR+SwNP in our survey seems to be acceptable.

282

283 *Impact of allergic rhinitis on asthma*

284 The increase in drug intake for rhinitis suggests an increase in severity from AR to
285 AR+SwNP [25]. Moreover, the association between the severity of the upper airway
286 diseases and their impact on asthma in the non adjusted analysis, seems to confirm the
287 United Airways Diseases hypothesis [1,26]. After adjusting for potential confounders, the
288 results show the presence of two different subsets of subjects within the AR group. The
289 first one includes subjects with AR and with sinusitis, and the second one those with
290 polyposis.

291 In the first group, the increase in the proportion of subjects who took drugs for rhinitis and
292 asthma suggests an increase in the severity of the upper airway diseases, which, does not
293 correspond to an increase in the indicators of asthma severity (at least one asthma attack)
294 and the ED visits for respiratory diseases.

295 Despite the increase in the drug intake in the group of subjects with polyposis, it is evident
296 that there is poor asthma control in this case.

297 We hypothesize that the positive answer to the question on the presence of nasal polyps
298 made it possible to identify two different asthma phenotypes in the AR subjects.

299 In the first one, “early onset allergic asthma phenotype”, the disease could be determined
300 by allergen-specific adaptative Th2 cells [27], and in the second one, “late onset
301 eosinophilic asthma phenotype” could be driven by allergen independent innate lymphoid
302 cells, and the responsiveness is characterized by refractory to steroids [28].

303 Although these two pathogenic mechanisms are not mutually exclusive, as confirmed by
304 the detection of allergic sensitization in patients with nasal polyposis, the role of the main
305 pathogenic mechanism seems to be clear [29].

306 When the severity of the upper airway diseases increased, a similar prevalence of the
307 most unstable subset of asthmatic subjects (about 3% of them) was unexpected. This may
308 be due to the poor adherence to the therapy [30].

309 Furthermore, the prevalence of poor control, even in subjects with the mildest asthma,
310 seems to be consistent with the recent studies on the presence of mast cells at the
311 alveolar level in subjects with allergic rhinitis and uncontrolled asthma [31-33].

312

313 **Strengths and Limitations**

314 The strength of this study is that we found the heterogeneity hidden in the diagnosis of
315 allergic rhinitis obtained from the questionnaire. This is in contrast to the simple model
316 used to compare allergic rhinitis and asthma (i.e. subjects with nasal polyp within those
317 with AR), and our finding suggests that their interaction should be considered with more
318 caution.

319 The main limitation of our survey is that we could not determine the allergic pathogenesis
320 of the upper airway diseases without cutaneous, serological [30] or any other clinical tests,
321 which also influence the reliability of the self-reported diagnosis of the upper airways
322 comorbidity, such as the diagnosis of chronic rhinosinusitis with and without polyps.
323 Another important limitation is the lack of any information about type, duration and the
324 adherence to the therapy for rhinitis and asthma. The only information available was if a
325 subject had used or not used drugs for rhinitis and/or asthma in the last 12 months.

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Competing Interests

The authors confirm that Gabriele Nicolini is an employee of the “Chiesi Farmaceutici, Parma, Italy,” one of the commercial funders of this research. There are no patents, products in development or marketed products to declare. All remaining authors declare that they have no competing interests.

Authors’ Contributions

Conceived and designed the experiments: Roberto de Marco. Pierpaolo Marchetti performed the data analysis. Leonardo Antonicelli, Pierpaolo Marchetti and Roberto de Marco wrote the paper. All the authors participated in the study design and in data collection and assembly, read and approved the final manuscripts.

371 **References**

- 372 1. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, Zuberbier
373 T, Baena-Cagnani CE, Canonica GW, van Weel C, Agache I, Ait-Khaled N, Bachert
374 C, Blaiss MS, Bonini S, Boulet LP, Bousquet PJ, Camargos P, Carlsen KH, Chen
375 Y, Custovic A, Dahl R, Demoly P, Douagui H, Durham SR, van Wijk RG, Kalayci
376 O, Kaliner MA, Kim YY, Kowalski ML, Kuna P, Le LT, Lemiere C, Li J, Lockey
377 RF, Mavale-Manuel S, Meltzer EO, Mohammad Y, Mullol J, Naclerio R, O'Hehir
378 RE, Ohta K, Ouedraogo S, Palkonen S, Papadopoulos N, Passalacqua
379 G, Pawankar R, Popov TA, Rabe KF, Rosado-Pinto J, Scadding GK, Simons
380 FE, Toskala E, Valovirta E, van Cauwenberge P, Wang DY, Wickman M, Yawn
381 BP, Yorgancioglu A, Yusuf OM, Zar H, Annesi-Maesano I, Bateman ED, Ben
382 Kheder A, Boakye DA, Bouchard J, Burney P, Busse WW, Chan-Yeung
383 M, Chavannes NH, Chuchalin A, Dolen WK, Emuzyte R, Grouse L, Humbert
384 M, Jackson C, Johnston SL, Keith PK, Kemp JP, Klossek JM, Larenas-Linnemann
385 D, Lipworth B, Malo JL, Marshall GD, Naspitz C, Nekam K, Niggemann
386 B, Nizankowska-Mogilnicka E, Okamoto Y, Orru MP, Potter P, Price D, Stoloff
387 SW, Vandenplas O, Viegi G, Williams
388 D; World Health Organization; GA(2)LEN; AllerGen.. Allergic Rhinitis and its Impact
389 on Asthma (ARIA) 2008 update (in collaboration with the World Health
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- 391 2. Bjerg A, Ekerljung L, Middelveld R, Dahlén SE, Forsberg B, Franklin K, Larsson
392 K, Lötval J, Olafsdóttir IS, Torén K, Lundbäck B, Janson C. Increased prevalence
393 of symptoms of rhinitis but not of asthma between 1990 and 2008 in Swedish
394 adults: comparisons of the ECRHS and GA²LEN surveys. PLoS One 2011; 17.
- 395 3. de Marco R, Cappa V, Accordini S, Rava M, Antonicelli L, Bortolami O, Braggion
396 M, Bugiani M, Casali L, Cazzoletti L, Cerveri I, Fois AG, Girardi P, Locatelli

- F,Marcon A, Marinoni A, Panico MG, Pirina P, Villani S, Zanolin ME, Verlato G; GEIRD Study Group. Trends in the prevalence of asthma and allergic rhinitis in Italy between 1991 and 2010. *Eur Respir J* 2012; 39: 883-892.
4. Mösges R, Hellmich M, Su VY, Chou KT, Liu CJ. Increased mortality in AR patients? *Allergy*. 2013;68:1209-10.
5. Magnan A, Meunier JP, Saugnac C, Gasteau J, Neukirch F. Frequency and impact of allergic rhinitis in asthma patients in everyday general medical practice: a French observational cross-sectional study. *Allergy* 2008; 63:292-298.
6. Price D, Zhang Q, Kocevar VS, Yin DD, Thomas M. Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. *Clin Exp Allergy* 2005; 35:282–287.
7. Olivieri M, Verlato G, Corsico A, Lo Cascio V, Bugiani M, Marinoni A, de Marco R; Italian European Community Respiratory Health Survey group. Prevalence and features of allergic rhinitis in Italy. *Allergy*. 2002;57:600-6.
8. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002; 109:419-425.
9. ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH, Rabe KF, Bel EH. Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J* 2005; 26:812-818
10. Ponte EV, Franco R and Nascimento HF, Souza-Machado A, Cunha S, Barreto ML, Naspitz C, Cruz AA. Lack of control of severe asthma is associated with co-existence of moderate-to-severe rhinitis. *Allergy* 2008; 63:564-569.
11. Lötval J, Ekerljung L and Lundbäck B. Multi-symptom asthma is closely related to nasal blockage, rhinorrhea and symptoms of chronic rhinosinusitis-evidence from the West Sweden Asthma Study. *Respir Res* 2010; 11:163.

- 422 12. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, Gjomarkaj M,
423 Forsberg B, Gunnbjornsdottir M, Minov J, Brozek G, Dahlen SE, Toskala E,
424 Kowalski ML, Olze H, Howarth P, Krämer U, Baelum J, Loureiro C, Kasper L,
425 Bousquet PJ, Bousquet J, Bachert C, Fokkens W, Burney P. Asthma in adults and
426 its association with chronic rhinosinusitis: the GA2LEN survey in Europe. *Allergy*.
427 2012; 67:91-98.
- 428 13. Bernstein JA. Allergic and mixed rhinitis: Epidemiology and natural history. *Allergy*
429 *Asthma Proc*. 2010;31:365-9.
- 430 14. Wilson KF, McMains KC, Orlandi RR. The association between allergy and chronic
431 rhinosinusitis with and without nasal polyps: an evidence-based review with
432 recommendations. *Int Forum Allergy Rhinol*. 2014 Jan 2. doi: 10.1002/alr.21258.
- 433 15. Antonicelli L, Braschi MC, Bresciani M, Bonifazi M, Baldacci S, Angino A, Pala
434 AP, Viegi G. The complex link between severity of asthma and rhinitis in mite
435 allergic patients. *Respir Med* 2013; 107:23-29.
- 436 16. de Marco R, Accordini S, Antonicelli L, Bellia V, Bettin MD, Bombieri C, Bonifazi
437 F, Bugiani M, Carosso A, Casali L, Cazzoletti L, Cerveri I, Corsico AG, Ferrari
438 M, Fois AG, Lo Cascio V, Marcon A, Marinoni A, Olivieri M, Perbellini L, Pignatti
439 P, Pirina P, Poli A, Rolla G, Trabetti E, Verlato G, Villani S, Zanolin ME; GEIRD
440 Study Group. The Gene-Environment Interactions in Respiratory Diseases (GEIRD)
441 Project. *Int Arch Allergy Immunol* 2010; 152:255-263.
- 442 17. de Marco R, Zanolin ME, Accordini S, Signorelli D, Marinoni A, Bugiani M, Lo
443 Cascio V, Woods R, Burney P. (1999) A new questionnaire for the repeat of the first
444 stage of the European Community Respiratory Health Survey: a pilot study. *Eur*
445 *Respir J* 14: 1044–1048.
- 446 18. Tahamiler R, Canakcioglu S, Ogreden S and Acioglu E. The accuracy of symptom-
447 based definition of chronic rhinosinusitis. *Allergy*. 2007 ;62:1029-1032.

19. Raheison C, Montaudon M, Stoll D, Wallaert B, Darras J, Chanez P, Crampette L, Magnan A, Demessi P, Orlando JP, Didier A, Serrano E, Prud'homme A, Meurice JC, Klossek JM, Tunon-de-Lara JM; SPLF Working Group "Nez-Bronches". How should nasal symptoms be investigated in asthma? A comparison of radiologic and endoscopic findings. *Allergy* 2004;59:821-826.
20. Tomassen P, Newson RB, Hoffmans R, Lötvald J, Cardell LO, Gunnbjörnsdóttir M, Thilising T, Matricardi P, Krämer U, Makowska JS, Brozek G, Gjomarkaj M, Howarth P, Loureiro C, Toskala E, Fokkens W, Bachert C, Burney P, Jarvis D. Reliability of EP3OS symptom criteria and nasal endoscopy in the assessment of chronic rhinosinusitis: a GA² LEN study. *Allergy* 2011; 66:556-561.
21. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, Bousquet PJ, Brozek G, Bruno A, Dahlén SE, Forsberg B, Gunnbjörnsdóttir M, Kasper L, Krämer U, Kowalski ML, Lange B, Lundbäck B, Salagean E, Todo-Bom A, Tomassen P, Toskala E, van Drunen CM, Bousquet J, Zuberbier T, Jarvis D, Burney P. Chronic rhinosinusitis in Europe--an underestimated disease. A GA²LEN study. *Allergy*.2011; 66:1216-23.
22. Wilson KF, McMains KC and Orlandi RR. The association between allergy and chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. *Int Forum Allergy Rhinol* 2014; 4:93-103.
23. Klossek JM, Neukirch F, Pribil C, Jankowski, Serrano E, Chanal I, El Hasnaoui A. Prevalence of nasal polyposis in France: a cross-sectional, case-control study. *Allergy*. 2005;60:233-237.
24. Ahmadi Afshar A, Farjd HR, Moezzi F, Mousavinasab N. Nasal polyposis in patients with asthma and allergic rhinitis. *J Laryngol Otol*. 2012; 126: 780-3.

25. Antonicelli L, Micucci C, Voltolini S, Senna GE, Di Blasi P, Visonà G, De Marco R, Bonifazi F. Relationship between ARIA classification and drug treatment in allergic rhinitis and asthma. *Allergy* 2007; 62:1064-1070.
26. Licari A, Caimmi S, Bosa L, Marseglia A, Marseglia GL, Caimmi D. Rhinosinusitis and asthma: a very long engagement. *Int J Immunopathol Pharmacol*. 2014; 27: 499-508.
27. [Suojalehto H](#), [Lindström I](#), [Majuri ML](#), [Mitts C](#), [Karjalainen J](#), [Wolff H](#), [Alenius H](#). Altered microRNA expression of nasal mucosa in long-term asthma and allergic rhinitis. [Int Arch Allergy Immunol](#). 2014;163(3):168-78.
28. Hekking PP, Bel EH. Developing and emerging clinical asthma phenotypes. *J Allergy Clin Immunol Pract*. 2014;2:671-80
29. Van Crombruggen K, Zhang N, Gevaert P, Tomassen P, Bachert C. Pathogenesis of chronic rhinosinusitis: inflammation. *J Allergy Clin Immunol*. 2011; 128:728-732
30. Corsico AG, Cazzoletti L, de Marco R, Janson C, Jarvis D, Zoia MC, Bugiani M, Accordini S, Villani S, Marinoni A, Gislason D, Gulsvik A, Pin I, Vermeire P, Cerveri I. Factors affecting adherence to asthma treatment in an international cohort of young and middle-aged adults. *Respir Med* 2007; 101:1363-1367
31. Scichilone N, Battaglia S, Taormina S, Modica V, Pozzecco E, Bellia V. Alveolar nitric oxide and asthma control in mild untreated asthma. *J Allergy Clin Immunol* 2013; 131:1513-1517.
32. Andersson CK, Tufvesson E, Aronsson D, Bergqvist A, Mori M, Bjermer L, Erjefält JS. Alveolar mast cells shift to an FcεRI-expressing phenotype in mild atopic asthma: a novel feature in allergic asthma pathology. *Allergy* 2011; 66:1590-1597.

- 497 33. Andersson CK, Bergqvist A, Mori M, Mauad T, Bjermer L, Erjefält JS. Mast cell-
498 associated alveolar inflammation in patients with atopic uncontrolled asthma. J
499 Allergy Clin Immunol 2011; 127:905-912.
- 500 34. Smith HE, Hogger C, Lallemand C, Crook D and Frew AJ. Is structured allergy
501 history sufficient when assessing patients with asthma and rhinitis in general
502 practice? J Allergy Clin Immunol 2009; 12:646-650.

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506 **TABLES AND FIGURES**
507

508 Table 1. Number of responders, response rate and prevalence of AR (with 95%CI) for
509 each participating centre.

| centers | n. of participating subjects (response rate (%)) | prevalence (95%CI) | | | |
|----------------|--|-------------------------|-------------------------|----------------------|----------------------|
| | | AR overall | AR only | AR+SsNP | AR+SwNP |
| Verona | 1746 (67,7) | 24.4 (22.4-26.5) | 17.8 (16.0-19.6) | 5.5 (4.5-6.8) | 1.1 (0.7-1.7) |
| Pavia | 966 (37,1) | 25.0 (22.2-27.8) | 18.7 (16.3-21.3) | 5.2 (3.9-6.8) | 1.0 (0.5-8.3) |
| Turin | 1205 (54,6) | 27.0 (24.4-29.6) | 21.0 (18.7-23.5) | 5.0 (3.8-6.4) | 0.9 (0.5-1.7) |
| Sassari | 1245 (53,0) | 25.7 (23.2-28.2) | 17.2 (15.2-19.4) | 6.7 (5.4-8.3) | 1.7 (1.1-2.6) |
| overall | 5162 (53,0) | 25.4 (24.2-26.6) | 18.6 (17.5-19.7) | 5.7 (5.0-6.3) | 1.2 (0.9-1.5) |

510 AR: Allergic Rhinitis; SsNP:Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal
511 Polyps
512 CI: Confidence Interval

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517 Table 2. characteristics of subjects stratified by presence of AR and different phenotypes
518 for subjects with AR

| variables | without AR | AR overall | | subjects with AR | | | p |
|---|---------------|---------------|--------------|------------------|-------------|-------------|------------------|
| | | | | AR only | AR+Ss NP | AR+Sw NP | |
| | n= 3795 | n= 1294 | p | n= 945 | n= 288 | n= 61 | |
| gender (%) | | | | | | | |
| <i>female</i> | 53.5 | 53.6 | 0.93 | 51.8 | 63.5 | 36.1 | <0.001 |
| age (%) | | | 0.041 | | | | 0.516 |
| <i><30</i> | 26.2 | 29.7 | | 30.4 | 29.5 | 19.7 | |
| <i>30-39</i> | 43.8 | 42.6 | | 42.0 | 43.4 | 49.2 | |
| <i>≥40</i> | 30.0 | 27.7 | | 27.6 | 27.1 | 31.1 | |
| smoking habits (%) | | | 0.048 | | | | 0.181 |
| <i>never smoker</i> | 54.7 | 57.6 | | 59.1 | 54.7 | 47.5 | |
| <i>ex-smoker</i> | 18.0 | 18.6 | | 17.2 | 22.1 | 23.0 | |
| <i>current smoker</i> | 27.3 | 23.8 | | 23.7 | 23.2 | 29.5 | |
| education (%) | | | 0.006 | | | | 0.019 |
| <i>primary and lower secondary school</i> | 23.4 | 19.2 | | 18.4 | 18.8 | 32.8 | |
| <i>upper secondary school</i> | 50.5 | 52.8 | | 52.0 | 57.5 | 42.6 | |
| <i>degree</i> | 26.1 | 28.1 | | 29.6 | 23.7 | 24.6 | |
| season (%) | | | 0.052 | | | | 0.237 |
| <i>spring</i> | 46.1 | 46.0 | | 47.3 | 42.0 | 44.3 | |
| <i>summer</i> | 15.4 | 15.0 | | 15.8 | 12.8 | 14.8 | |
| <i>autumn</i> | 32.4 | 30.7 | | 28.7 | 37.2 | 31.1 | |
| <i>winter</i> | 6.1 | 8.3 | | 8.2 | 8.0 | 9.8 | |

519 AR: Allergic Rhinitis; SsNP:Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal
520 Polyps

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Table 3. crude prevalence (%) of different symptom or condition of asthma and drugs used in the last 12 months among subjects with allergic rhinitis, sinusitis and polyposis.

| Conditions | AR overall | AR only | AR+SsNP | AR+SwNP | p |
|---|------------|---------|---------|---------|--------|
| Physician-diagnosed asthma | 23.8 | 23.0 | 24.8 | 31.7 | 0.28 |
| Current asthma | 17.5 | 15.8 | 20.1 | 31.2 | <0.01 |
| At least 1 asthma attack | 11.5 | 10.2 | 13.9 | 21.3 | 0.01 |
| >3 asthma attacks | 3.2 | 3.0 | 3.9 | 3.3 | 0.76 |
| Asthma-COPD overlap syndrome | 3.0 | 2.6 | 3.2 | 8.6 | 0.03 |
| Drugs for asthma used in the last 12 months | 17.5 | 15.2 | 22.4 | 29.3 | 0.001 |
| Cough and phlegm | 22.7 | 17.9 | 34.9 | 40.7 | <0.001 |
| ED admissions for respiratory diseases | 1.1 | 0.8 | 1.4 | 5.1 | <0.01 |
| Drugs for rhinitis used in the last 12 months | 54.0 | 48.9 | 65.2 | 70.5 | <0.001 |

AR: Allergic Rhinitis; SsNP: Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal Polyps

ED: Emergency Department

534 Table 4. Association of different symptom or condition of asthma and among subjects with
 535 allergic rhinitis, sinusitis and polyposis. (Relative Risk Ratio (RRR*) and 95%CI)

| Conditions | AR only | AR+SsNP | AR+SwNP |
|---|---------|-------------------------|--------------------------|
| | | RRR (95%CI) | RRR (95%CI) |
| Physician-diagnosed asthma | 1 | 1.11 (0.81-1.52) | 1.48 (0.83-2.64) |
| Current asthma | 1 | 1.35 (0.95-1.91) | 2.31 (1.29-4.15) |
| At least 1 asthma attack | 1 | 1.39 (0.93-2.08) | 2.30 (1.19-4.46) |
| >3 asthma attacks | 1 | 1.26 (0.61-2.61) | 1.03 (0.23-4.54) |
| Asthma-COPD overlap syndrome | 1 | 1.08 (0.49-2.40) | 2.71 (0.96-7.67) |
| Drugs for asthma used in the last 12 months | 1 | 1.52 (1.08-2.15) | 2.27 (1.23-4.19) |
| Cough and phlegm | 1 | 2.59 (1.89-3.54) | 2.91 (1.63-5.21) |
| ED admissions for respiratory diseases | 1 | 1.91 (0.54-6.71) | 5.61 (1.81-23.92) |
| Drugs for rhinitis used in the last 12 months | 1 | 1.91 (1.43-2.54) | 2.46 (1.38-4.40) |

536 *adjusted for gender, age, smoking habits, level of education, season of response, centre,
 537 type of contact and percentile rank of cumulative response.

538 AR: Allergic Rhinitis; SsNP:Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal
 539 Polyps
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541 ED: Emergency Department

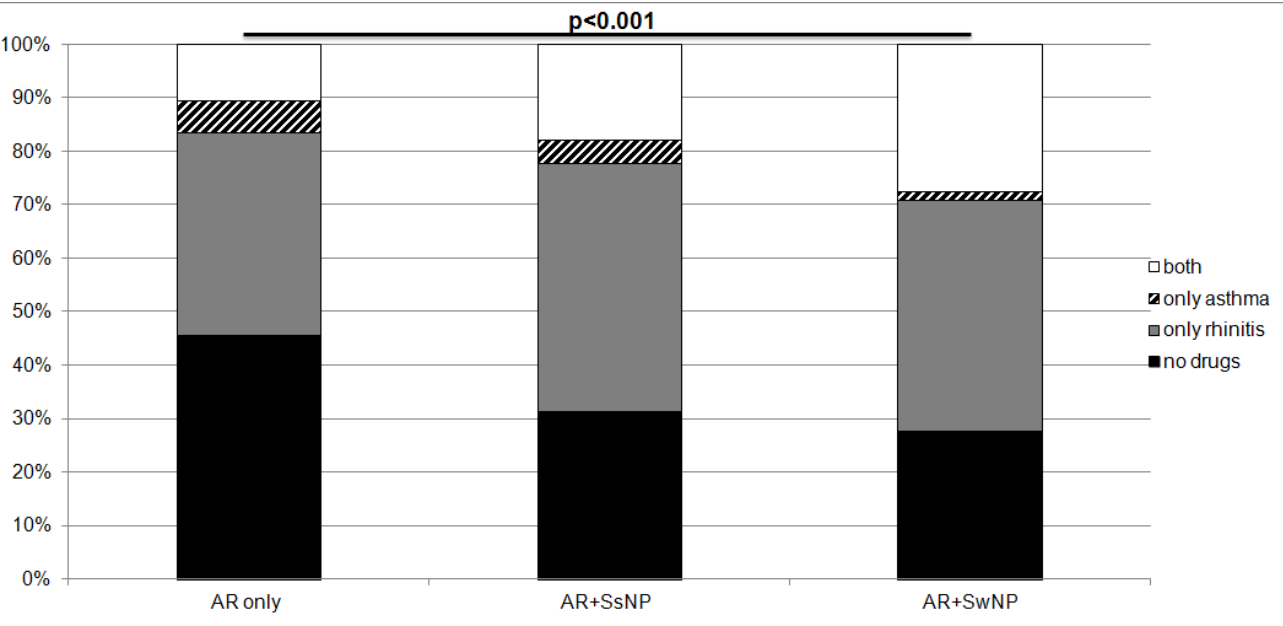
542 RRR: Relative Risk Ratio

543 CI: Confidence Interval

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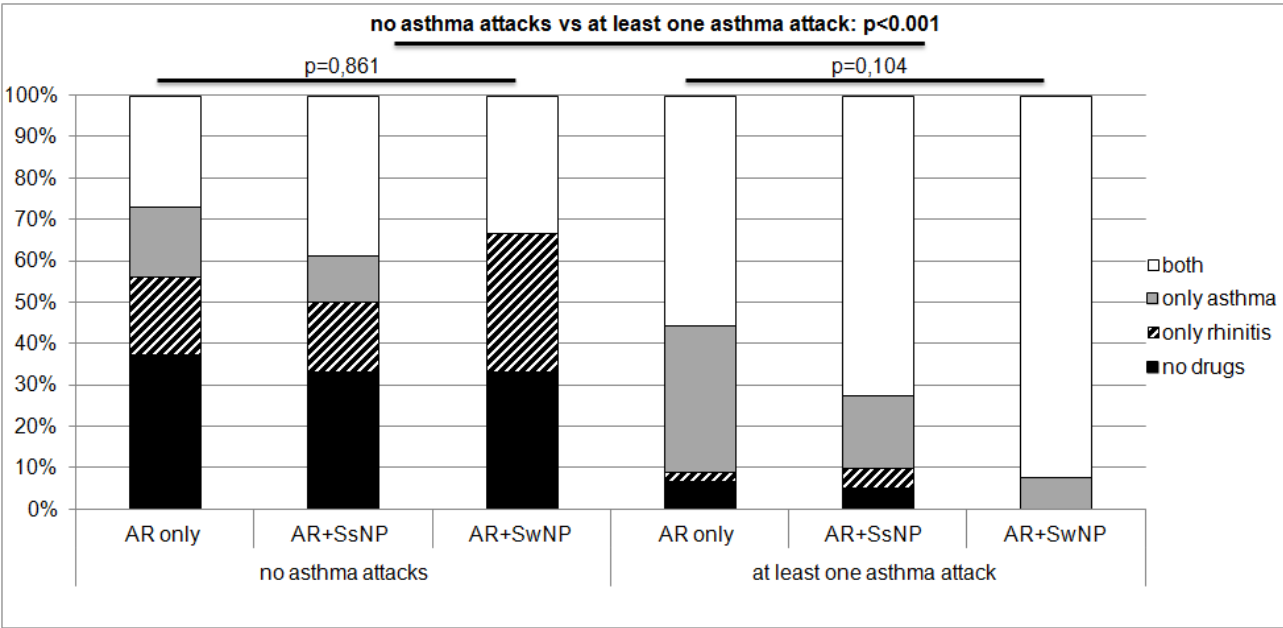
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546 Figure 1. Distribution of subjects who used medication for rhinitis and asthma or both in
547 the last 12 months stratified by categories of rhinitis



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550 AR: Allergic Rhinitis; SsNP: Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal
551 Polyps
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558 Figure 2. Distribution of subjects with allergic rhinitis who used medication for rhinitis and
559 asthma in the last 12 months stratified by categories of rhinitis and asthma attacks



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561 AR: Allergic Rhinitis; SsNP: Sinusitis without Nasal Polyps; SwNP= Sinusitis with Nasal
562 Polyps
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